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Newcastle University

Health Technology Briefing
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Duvelisib for treating relapsed and/or refractory peripheral T-cell lymphoma

Company/Developer	Secura Bio

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29009	NICE ID: 10745	UKPS ID: 663329

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Duvelisib is in development for relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL), a group of lymphomas (cancer that begins in cells of the immune system), that develop from mature T-cells, which are a type of white blood cell. Relapsed means that the disease has reappeared after a period of remission; refractory is used to describe when the lymphoma does not respond to treatment. In the past, PTCLs have been treated with medicines used for B cell lymphomas, a more common type of blood cancer; but these medicines don't work as well in PTCL. There is a need for new treatments with are proven to work in PTCL, which can control cancer growth and help people with PTCL to live longer.

Duvelisib is an oral treatment taken twice per day. Duvelisib blocks the effects of certain enzymes (called PI3K-delta and PI3K-gamma) that are overactive in blood cancers. These enzymes enable the growth and survival of the cancer cells. By blocking the effects of the enzymes, duvelisib causes the cancer cells to die, thereby delaying or stopping the progression of the cancer. Initial trial results show duvelisib has a benefit in controlling PTCL in patients who have not responded to previous treatment, usually a combination of chemotherapy agents. If licensed, duvelisib might provide a treatment option for patients with R/R PTCL who do not have many options available.

Proposed Indication

Duvelisib for relapsed or refractory (R/R) peripheral T-cell lymphoma (PTCL).[1,2]

Technology

Description

Duvelisib (Copiktra, ABBV-954, INK-1197, IPI-145) is an oral, dual inhibitor of phosphoinositide 3-kinase-δ (PI3K-δ) and PI3K-γ. PI3K-δ and PI3K-γ are frequently found to be activated in haematological malignancies and play distinct roles in tumorigenesis; PI3K-δ signalling driving tumour cell proliferation, and PI3K-γ drives migration and differentiation of support cells in the tumour microenvironment.[3]

Duvelisib is in phase II clinical trials for R/R PTCL, as a twice daily oral treatment (PRIMO; NCT03372057). The study has 2 phases, a dose optimization phase and an expansion phase.

In the Dose Optimization Phase, patients will be randomly assigned to 1 of 2 study cohorts, as follows:

- Cohort 1: Duvelisib per oral (PO) twice a day (BID) at a starting dose of 25 mg, with potential escalation on a per-patient basis to 50 mg and then 75 mg, based on the patient's response to and tolerance of therapy, in 28-day cycles.
- Cohort 2: Duvelisib 75 mg PO BID, administered in 28-day cycles.

Based upon results of the dose optimization phase, patients in the dose escalation phase received a starting dose of 75mg to achieve rapid tumour response, followed by 25mg twice daily as a maintenance therapy, in 28-day treatment cycles.[4-6]

Key Innovation

Duvelisib is a first-in-class dual inhibitor of PI3K-δ and PI3K-γ in development for a number of advanced haematological malignancies, including R/R PTCL. Treatment approaches for PTCLs have traditionally been based upon those in B-cell lymphomas, though with inferior outcomes, and prognosis remains poor in PTCLs. There is a need for additional therapy options which show an improved clinical benefit in R/R PTCLs.[7] Initial results from ongoing and completed phase I/II clinical trials indicate duvelisib may offer clinical benefit in R/R PTCL.[5,6,8,9]

Regulatory & Development Status

Duvelisib received EU Marketing Authorisation in May 2021 as a monotherapy for R/R chronic lymphocytic leukaemia (CLL) or follicular lymphoma (FL) after two prior therapies.[10]

Duvelisib is in phase II clinical development for:[2]

- T-Cell Lymphoma
- Indolent B-Cell Lymphoma
- COVID-19
- Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- Asthma
- Rheumatoid Arthritis
- Melanoma

Duvelisib is in phase III clinical development as a monotherapy for R/R CLL/ small lymphocytic lymphoma (SLL).[1,4,11]

Patient Group

Disease Area and Clinical Need

PTCL is a heterogeneous group with over 20 distinct lymphomas that develop from mature T-cells or natural killer (NK) cells. Symptoms of PTCL vary but can include fatigue, painless swelling in the armpit or groin, night sweats, rash and weight loss. PTCLs occur anytime during adulthood but are most common in people older than 60 years (median age at diagnosis is 65.7).[12-14]

PTCLs are relatively rare, occurring in 0.9 per 100,000 people in the UK, with around 580 new cases expected each year.[14] The WHO classification groups PTCLs as nodal, extra nodal or leukaemic.[13] In Europe, nodal PTCLs account for >80% PTCL cases; including, 34% PTCL not otherwise specified (PTCL-NOS), 28% angioimmunoblastic T-cell lymphomas (AITL) and 15% anaplastic large cell lymphoma (ALCL) ALK+/-.[15]

PTCLs continue to be associated with poor prognosis, with a median overall survival (OS) of around 6 months and limited progression free survival (PFS).[5,7] Prognosis varies significantly by subtype, however across PTCLs as a group, survival rates are 56.9% at 1 year, 40.4% at 3 years and 34.9% at 5 years.[16] In England, in 2021-21, there were 4246 finished consultant episodes (FCE) and 3812 admissions for Mature T/NK-cell lymphomas (ICD-10 code C84.4) which resulted in 2925 day cases and 2973 FCE bed days.[17]

Recommended Treatment Options

Current ESMO guidelines (2015) outline the following treatment options for R/R PTCL:[15]

- Autologous or allogenic stem cell transplant (autoSCT, alloSCT), potentially curative in this setting
- Palliative radiotherapy may be used to manage local symptomatic disease
- Chemotherapy combination regimens, such as DHAP (dexamethasone, high-dose cytarabine, cisplatin) or ICE (ifosphamide, etoposide, carboplatin); may be attempted in chemo-sensitive patients, with the aim for patient to receive potentially curative alloSCT
- In less fit patients, chemotherapy monotherapies may be used, such as gemcitabine or bendamustine which are generally well-tolerated

Clinical Trial Information

Trial	**PRIMO, NCT03372057, 2019-001123-13;** A Multi-Center, Phase 2, Open-label, Parallel Cohort Study of Efficacy and Safety of Duvelisib in Patients With Relapsed or Refractory Peripheral T Cell Lymphoma (PTCL) **Phase II** – Recruiting **Locations:** 2 EU countries, UK, and USA **Primary completion date:** March 2022
Trial Design	Randomized, sequential assignment, open label
Population	N= 120 participants (planned), patients with R/R PTCL, 18 years and older
Intervention(s)	Duvelisib, oral, twice daily
Comparator(s)	No comparator

Outcome(s)	**Primary endpoints:** • Overall Response Rate (ORR) • Best response of Complete Response (CR) or Partial Response (PR)
Results (efficacy)	Results of the dose-optimization phase (N=33) showed a 54% ORR in the 75 mg BID (N=13) and 35% in the 25 mg BID (N=20) cohorts.[5] Latest results from the PRIMO dose-expansion cohort (75 mg BID followed by 25 mg BID dosing) (N=8) show an ORR of 50 % and CR rate of 32.1% with a median duration of response of 233 days.[9]
Results (safety)	Latest results from the PRIMO dose-expansion cohort (75 mg BID followed by 25 mg BID dosing) (N=78): • There were 3 deaths related or possibly related to duvelisib: pneumonitis, Epstein-Barr associated lymphoproliferative disorder, and sepsis • The most frequent > Grade 3 adverse events seen were neutropenia (38.5%), alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased (24.4%/ 21.8%), rash (7.7%), lymphocyte count decreased (7.7%), and sepsis (6.4%). ALT and/or AST elevations were the most common adverse events (AEs) leading to treatment discontinuations (N=12, 15.4%) • Discontinuation due to AEs (N=15, 19.2%).[9]

Estimated Cost

The cost of duvelisib is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- ESMO Guidelines Committee. (2015). Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[15]
- British Committee for Standards in Haematology. Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma). Updated August 2013.[18]

Additional Information

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References

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